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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,724	10/27/2003	Joseph Loscalzo	102258.170 US3	9697

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EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 07/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,724	LOSCALZO ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *12-20 and 23-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 21-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/28, 9/2&11/15/4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS7/05/05*.

DETAILED ACTION

1. Applicants' response filed 21 April 2006 to Office Action mailed 29 March 2006 is acknowledged and entered.

2. To ensure that all papers filed in a response remain together and for an expedient communication, especially during a telephone inquiry/interview to a response /amendment filed to an Office Action, Examiner will very much appreciate that in response to this Office Action, applicants label the header at each page of said response/amendment with U.S. Non-Provisional Application Serial number, U.S. Non-Provisional application filing date, Attorney's Docket number, First Applicant's name, Document Page number, Group Art Unit Number and Examiner's name. This practice immensely minimizes the papers lost during transaction/transmission and facilitates examination.

Claims Status

3. Claims 1-37 are pending

Restriction/Election

4. Applicants' election with traverse of Group I, Claims 2-11 and 21-22, filed 21 April 2006 to election requirement in Office Action mailed 29 March 2006 is acknowledged and entered. Despite the election being made with traverse, applicants have not presented any arguments traversing said election. Therefore, the restriction requirement is deemed proper and is made FINAL.

5. Claim 1 is a linking Claim and is therefore examined together with Group I election. Accordingly, Claims 12-20 and 23-37 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03. Examiner suggests that the non-elected Claims 1, 12-20 and 23-36 cited *supra* be canceled in response to this Office action to expedite further prosecution.

6. Claims 1-11 and 21-22 are examined on merits.

Priority

7. Applicants' claim for domestic priority under 35 U.S.C.§ 119(e) to Provisional U.S. Applications 60/162,230 and 60/179,020 filed on 10/29/ 1999 and 1/31/2000 respectively is acknowledged.

8. Applicants' Claim for domestic priority under 35 U.S.C.§ 120 to Non-provisional U.S. application,

10/679,257 filed 10/07/2003 is acknowledged.

9. Applicants' Claim for domestic priority under 35 U.S.C.§ 121 to Non-provisional U.S. application 09/697,317 filed 10/27/2000, now U.S. Patent 6,635,273 is also acknowledged.

Information Disclosure Statement

10. Applicants' Information Disclosure Statements (i.e., IDSs) filed 28 January 2004, 02 September 2004 15 November 2004 and 05 July 2005 have been made of record and considered.

Objection to Information Disclosure Statement

11. Applicants' Information Disclosure Statement (i.e., IDS) filed 27 October 27, 2003 is objected to because the application number on forms 1449 labeled as Pages 2-5 accompanying said IDS is different than that of the instant application. Said IDS has been placed in file but references cited therein have not been considered. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 103

12. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C.§ 103(a).

14. Claims 1-10 and 21-22 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Birch et al (U.S. Patent 5,627,191) in view of Cohn (U.S. Patent 4,868, 179).

Claims recite a method to treat a nitric oxide insufficiency mediated disease via administering a composition comprising at least one nitrosated angiotensin converting enzyme inhibitor, wherein said disease is a cardiovascular disease among congestive heart failure, hypertension etc. Said composition is one of a nitrosated "pril" compound.

Birch et al. teach a method to treat a cardiovascular disease via administering a composition comprising angiotensin II antagonist activity, wherein said disease is hypertension (Abstract). Said composition also comprises hydralazine hydrochloride (Column 33, Lines 56-65; Column 34, Lines 1-3). Birch et al., do not clearly teach the presence of isosorbide dinitrate in their composition/method. Cohn, teaches a composition comprising isosorbide dinitrate, digoxin and thiazide in addition to hydralazine hydrochloride (Column 2, Lines 26-60, Column 3, Lines 1-35). Said composition is intrinsically applicable to treat cardiovascular disease.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Birch et al. according to beneficial teachings from Cohn et al. to obtain a method to treat a nitric oxide insufficiency mediated disease via administering a composition comprising at least one nitrosated angiotensin converting enzyme inhibitor (i.e., hydralazine hydrochloride and isosorbide dinitrate) wherein said disease is a cardiovascular disease among congestive heart failure, hypertension etc .

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Birch et al. according to beneficial teachings from Cohn et al. to obtain a method to treat a cardiovascular disease, e.g., hypertension as discussed *supra.*

Thus, the cited references clearly show that at the time of the invention, a method to treat cardiovascular disease by administering a composition comprising angiotensin II antagonist activity, hydralazine hydrochloride, digoxin, isosorbide dinitrate and thiazide. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 U.S.C. § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

16. Claims 1-11 and 21-22 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method to administer an antioxidant comprising composition in patients having hypertension via instantly claimed method of administering the instantly claimed pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification, while being enabling for a method to treat hypertension, does not particularly illustrate an example of a method to preventing "nitric oxide insufficiency mediated vascular disease via administering a composition comprising hydralazine salts in mixtures with one of isosorbide di- or mononitrate in combination with a pharmaceutically acceptable carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

From the record of the present written disclosure applicants have merely mentioned administering a variety of compositions comprised of hydralazine salts in mixtures with one of isosorbide di- or mononitrate to treat a cardiovascular disease, e.g., hypertension.

Inventions targeted for human therapy claiming method(s) of treatment and/or prevention of a certain ailment bear a heavy responsibility to provide supporting evidence because of the unpredictability of the biological responses to therapeutic treatments. THE STANDARD OF ENABLEMENT IS HIGHER FOR SUCH INVENTIONS because effective prevention or prophylaxis of disease conditions are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to human that would in effect "prevent" the disease condition/ailment from happening require supporting evidence because of the unpredictability in biological responses to therapeutic treatments or therapeutic prophylaxis. In order to enable the skilled artisan to practice the invention as claimed, applicants would have to demonstrate the functional effect and describe the therapeutic effect or prophylactic effect, and describe the effective amounts of each ingredient of the composition for the administration of the composition intended for a method of therapeutic treatment or prophylaxis. THERE IS NO GUIDANCE IN THE SPECIFICATION, other

than a method to administer a composition comprising one of isosorbide di- or mononitrate in combination with a pharmaceutically acceptable carrier for the treatment and/or prevention of aforementioned disease conditions. MOREOVER, THE INSTANT APPLICATION DOES NOT PROVIDE A WORKING EXAMPLE PROVIDING DATA THAT SHOWS THAT THE METHOD AND COMPOSIOTION OF THE INSTANTLY CLAIMED INVENTION WOULD INDEED PREVENT AN EVENT SUCH AS THE CLAIM DESIGNATED DISEASE CONDDITIONS. THUS, APPLICANTS HAVE NOT DEMONSTRATED THE CLAIMED FUNCTIONAL EFFECT OF PREVENTING ANY AND ALL LOW-RENIN HYPERTENSION, SALT-SENSITIVE HYPERTENSION OR LOW-RENIN, SALT SENSITIVE HYPERTENSION.

Accordingly, undue experimentation without a reasonable expectation of success as to how to determine which combination of each of the claims designated pharmaceutical compositions in mixtures with one of isosorbide di- or mononitrate in combination with a pharmaceutically acceptable carrier in which therapeutic amounts of any or all of the claimed designated components would be effective in the instantly claimed method to administer the instantly claimed composition to obtain the instantly claimed functional effect of treating and/or preventing a cardiovascular disease, e.g., hypertension would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Conclusion

17. For reasons aforementioned, no Claims are allowed.

However, Claim 11 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. §112, 1st paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Terry McKelvey, can be reached on (571)-272-0775 Monday through Friday 8:00 A.M. to 4:30 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for

unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). Alternatively, status inquiries should be directed to the receptionist whose telephone number is (703) 308-0196.

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July 10, 2006

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